PATENT
2081-0413P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	JORGENSEN, Kent et al.	Conf.:	3281
Appl. No.:	09/781,893	Group:	1615
Filed:	February 9, 2001	Examiner:	Gollamudi KISHORE

For: LIPID-BASED DRUG DELIVERY SYSTEMS CONTAINING PHOSPHOLIPASE A2 DEGRADABLE LIPID DERIVATIVES AND THE THERAPEUTIC USES THEREOF

REPLY UNDER 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, DC 20231

December 4, 2002

Sir:

In response to the Examiner's Office Action issued September 4, 2002, the following amendments and remarks are respectfully submitted in connection with the above-identified application.

REMARKS

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1-11, 14-21 and 23-24 as obvious over Kozak (USP 6,166,089) in combination with Janjic (USP 6,229,002) and Vermehren (BBA, 1998). The Examiner contends that Kozak discloses phospholipid prodrugs where carbon 1 of the glycerol has an aliphatic chain, the carbon 2 has an

organic radical and carbon 3 has a phosphatidyl group. The Examiner indicates that Kozak teaches the organic radical is released by phopholipase A2 (PLA2) present in the pathological tissue. The Examiner acknowledges that Kozak lacks the teaching of a lipopolymer and the administration of the composition in the form of liposomes.

The Examiner also contends that Janjic teaches several advantages of administration of lipid constructs in the form of liposomes and attaching PEG to the liposomal surface to shield the liposomal complex from blood protein. This extends its circulation period in the blood stream. The Examiner also asserts that Janjic teaches that the prodrug is on the outside surface of the liposomes.

The Examiner further contends that Vermehren teaches that PEG not only provides steric hindrance which leads to a decrease in the absorption and interaction of plasma degrading proteins with the liposomal surface, but also enables PLA2 to have increased catalytic activity on the phospholipid containing lipsomes. According to the Examiner, Vermehren suggests that it is possible to design and optimize the *in vivo* degradation of drug loaded liposomes at certain sites, for example due to an enhanced local concentration of active PLA2 and an accumulation of polymer-grafted liposomes in the tissue.

The Examiner concludes that it would have been obvious to a skilled artisan to use PEG containing liposomes for the delivery of the prodrug described by Kozak because of the advantages of liposomes and the ability of PEG to prolong the circulation time of the liposomes. He also contends that this would increase the liposomes susceptibility to PLA2 in the host pathological tissue and increase the release of the drug attached to carbon 2 of the phospholipid as described in Kozak. Applicants respectfully traverse.

Applicants respectfully submit that there are several differences between Kozak and the present invention apart from the absence of a lipopolymer and the administration of the composition in the form of liposomes. For example, Kozak teaches that the radical in the sn-2 position is the active drug which is a low molecular weight radical linked to phosphatidylcholine. The drugs are released intracellularly from the monomeric lipid prodrug substrate by the action of intracellular PLA2. Therefore, the prodrugs have to be able to penetrate the cell wall as monomeric lipid prodrugs. As a consequence, the prodrugs are not formulated as particles and not as liposomes. In fact, Kozak teaches away from formulating the prodrugs into liposomes (see column 6, lines 4-6).

More importantly, the prodrugs disclosed in Kozak have acyl-linked groups on both carbon 1 and carbon 2. In the

present invention, however, anticancer lysolipids, such as ether lysolipids, constitute the lysolipid part of the prodrug phospholipid. Furthermore, Kozak teaches that intracellular PL2 will be able to hydrolyze diacyl phospholipids, but there is no indication or suggestion that this would also be true for the hydrolysis of phospholipids with, for example, ether-linked alkyl chains in the sn-1.

Kozak does not teach that anticancer lysolipids comprised in a glycerophospholipid will be non-toxic and that a lysolipid resulting from the hydrolysis of an acyl-linked radical in the sn-2 position will regain its toxicity. Neither does Kozak disclose or suggest that such mono-ester and mono-ether prodrug phospholipids can be incorporated into liposomal bilayers. In addition, Kozak does not teach that increasing the length of circulation in the blood stream will result in the delivery of the active drug to the desired tissue in which extracellular PLA2 activity is increased.

These features of the present invention which are missing from Kozak are not disclosed in Janjic and Vermehren. Janjic relates to a DNA-ligand attached to PEG resulting in improved pharmacokinetics, whereas Vermehren discloses enhanced hydrolysis of PEG containing liposomes. Neither of these references discloses using the anti-cancer lysolipids as part of the lipid prodrug. The mere disclosure of some, but not all,

features in separate documents without any indications or suggestion that such features could be combined with a reasonable expectation of success to arrive at the instant invention does not support a conclusion of obviousness. As stated above, the Kozak reference actually teaches away from the use of liposomes, which is a critical feature of the instant invention. In view of this and the discussion above, Applicants respectfully request reconsideration and removal of the rejection.

In view of the above remarks, all of the claims remaining in the case are submitted as defining non-obvious, patentable subject matter.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. No. 30,330) at 714-708-8555 in Costa Mesa, CA to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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2081-0113P

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope to: Commissioner of Patents and Trademarks, Washington D.C. 20231 on: December 4, 2002
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BIRCH, STEWART, KOLASCH & BIRCH, LLP

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